# APPENDIX
## Characteristics of Available Antiretroviral Drugs

## Nucleoside/Nucleotide Analogue Reverse Transcriptase Inhibitors (NRTIs/NtRTIs)* †

### *Abacavir (GW 1592U89, ABC, Ziagen™)*

**URL: Link to Pediatric Antiretroviral Drug Information**

*Preparations: Pediatric oral solution:* 20 mg/mL; Tablets: 300 mg

*Tablets in combination with zidovudine and lamivudine:* TRIZIVIR- 300 mg zidovudine , 150 mg lamivudine, and 300 mg abacavir.

**Dosage**

*Neonatal/Infant dose:* Not approved for infants less than three months of age. In infants between one and three months of age, a dose of 8 mg/kg of body weight twice daily is under study.

*Pediatric/Adolescent dose:* 8 mg/kg of body weight twice daily, maximum dose 300 mg twice daily.

*Adult dose:* 300 mg twice daily.

*Adult dose of TRIZIVIR:* 1 tablet twice daily.

**Major Toxicities**

*More common:* Nausea, vomiting, fever, headache, diarrhea, rash, and anorexia.

*Less common (more severe):* Approximately 5% of adults and children receiving ABC develop a potentially fatal hypersensitivity reaction. Symptoms include fever, fatigue, malaise, nausea, vomiting, diarrhea, and abdominal pain or respiratory symptoms such as shortness of breath. Physical findings include lymphadenopathy, ulceration of mucous membranes, and maculopapular or urticarial skin rash. The hypersensitivity reaction can occur without a rash. Laboratory abnormalities include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, and lymphopenia. This reaction generally occurs in the first six weeks of therapy. Patients suspected of having a hypersensitivity reaction should have ABC stopped and not restarted since hypotension and death have occurred upon rechallange. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.

*Rare:* Pancreatitis, increased liver enzymes, elevated blood glucose, elevated triglycerides, and fatigue.

**Drug Interactions**

- No significant interactions between ABC, ZDV, and 3TC.
- ABC does not inhibit, nor is it metabolized by, hepatic cytochrome P450 enzymes. Thus, it should not cause changes in drug levels or clearance of agents metabolized through these pathways, such as PIs and NNRTIs.
- Ethanol decreases elimination of ABC, resulting in a modest increase in drug exposure.

**Special Instructions**

- Can be given without regard to food.
- Patients and parents must be cautioned about the risk of serious hypersensitivity reaction. A medication guide and warning card should be provided. Patients experiencing a hypersensitivity reaction should be reported to the Abacavir Hypersensitivity Registry (1-800-270-0425).
- Patients should not interrupt therapy without consulting with their physician.

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* Information in this appendix is not all inclusive. Complete and detailed prescribing and toxicity information on these drugs is available from the drug companies and should be reviewed by the health care provider before prescribing these drugs.

† Adolescents in early puberty (Tanner I-II) should be dosed using pediatric schedules, whereas those in late puberty (Tanner Stage V) should be dosed using adult schedules. Youth who are in the midst of their growth spurt (Tanner III females and Tanner IV males) should be closely monitored for medication efficacy and toxicity when choosing adult or pediatric dosing guidelines.

## *Didanosine (dideoxyinosine, ddI, Videx®)*

**URL: Link to Pediatric Antiretroviral Drug Information**

*Preparations:* Pediatric powder for oral solution (when reconstituted as solution containing antacid): 10 mg/mL; Chewable tablets with buffers: 25, 50, 100, 150 mg, and 200mg; Buffered powder for oral solution: 100, 167, and 250 mg; Delayed-release capsules (enteric-coated beadlets): VIDEX EC- 125, 200, 250, and 400 mg.

**Dosage**

*Neonatal/Infant dose (infants aged <90 days):* 50 mg per $m^2$ of body surface area every 12 hours.

*Pediatric usual dose:* In combination with other antiretrovirals: 120 mg per $m^2$ of body surface area every 12 hours.

*Pediatric dosage range:* 90 to 150 mg per $m^2$ of body surface area every 12 hours (Note: may need higher dose in patients with central nervous system disease.)

*Adolescent/Adult dose:* Body weight ≥60 kg: 200 mg twice daily. Body weight <60 kg: 125 mg twice daily. May be administered once daily in adolescents/adults to improve compliance, however, twice daily dosing provides better therapeutic response than once daily dosing.

*VIDEX EC:* Adolescent/Adult dose: Body weight > 60 kg: 400 mg once daily. Body weight < 60 kg: 250 mg once daily.

**Major Toxicities**

*More common:* Diarrhea, abdominal pain, nausea, and vomiting.

*Less common (more severe):* Peripheral neuropathy (dose related), electrolyte abnormalities, and hyperuricemia. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.

*Rare:* Pancreatitis (dose related, less common in children than adults), increased liver enzymes, and retinal depigmentation.

**Drug Interactions**

- Possible decrease in absorption of ketoconazole, itraconazole, and dapsone; administer at least two hours before or two hours after ddI.
- Tetracycline and iron salts should be given one hour before or four hours after ddI.
- Fluoroquinolone antibiotic absorption significantly decreased (chelation of drug by antacid in pediatric powder and tablets); administer two hours before or four to eight hours after ddI (varies with fluoroquinolone antibiotic).
- Concomitant administration of ddI and DLV may decrease the absorption of these drugs; separate dosing by at least two hours.
- Administration with PIs: IDV should be administered at least one hour before ddI on an empty stomach. RTV should be administered at least two hours before or after ddI. NFV should be administered at least one hour after ddI.
- Tenofovir should be administered two hours before or one hour after ddI. The combination may cause increased ddI levels and therefore a higher risk of toxicity.

**Special Instructions**

- ddI formulation contains buffering agents or antacids.
- Food decreases absorption; administer ddI on an empty stomach (30 minutes before or two hours after a meal). Further evaluation in children regarding administration with meals is under study.
- For oral solution: shake well and keep refrigerated; admixture is stable for 30 days.
- When administering chewable tablets, at least two tablets should be administered to ensure adequate buffering capacity (i.e., if the child's dose is 50 mg, administer two 25 mg tablets and not one 50 mg tablet).
- Buffered powder is not suitable for once daily dosing except in patients with renal impairment.
- Decreased dosage should be used for patients with impaired renal function.

## *Lamivudine (3TC, Epivir®, Epivir HBV®)*

**URL: Link to Pediatric Antiretroviral Drug Information**

*Preparations:* Solution: 5 mg/mL (Epivir HBV), 10 mg/mL; Tablets: 100 (Epivir HBV), 150, 300 mg.

*Tablets in combination with zidovudine:* COMBIVIR–300 mg zidovudine and 150 mg lamivudine.
*Tablets in combination with zidovudine and abacavir:* TRIZIVIR- 300 mg zidovudine, 150 mg lamivudine, and 300 mg abacavir.

**Dosage**
*Neonatal dose (infants aged <30 days):* 2 mg per kg of body weight twice daily.

*Pediatric dose:* 4 mg per kg of body weight twice daily.

*Adolescent/Adult dose:* Body weight ≥50 kg: 150 mg twice daily or 300 mg once daily. Body weight <50 kg: 2 mg per kg of body weight twice daily.

*Adolescent/Adult dose of COMBIVIR:* one tablet twice daily.

*Adolescent/Adult dose of TRIZIVIR:* one tablet twice daily.

**Major Toxicities**
*More common:* Headache, fatigue, nausea, diarrhea, skin rash, and abdominal pain.

*Less common (more severe):* Pancreatitis (primarily seen in children with advanced HIV infection receiving multiple other medications), peripheral neuropathy, decreased neutrophil count, and increased liver enzymes. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.

**Drug Interactions**
- Trimethoprim/sulfamethoxazole (TMP/SMX) increases 3TC blood levels (possibly competes for renal tubular secretion); unknown significance.
- When used with ZDV may prevent emergence of ZDV resistance, and for ZDV-resistant virus, revision to phenotypic ZDV sensitivity may be observed.

**Special Instructions**
- Can be administered with food.
- For oral solution: store at room temperature.
- Decrease dosage in patients with impaired renal function.

## *Stavudine (d4T, Zerit®, Zerit XR®)*

**URL: Link to Pediatric Antiretroviral Drug Information**

*Preparations:* Solution:1 mg/mL; Capsules: 15, 20, 30, and 40 mg; Extended-release capsules (Zerit XR): 75 and 100 mg.

**Dosage**
*Neonatal dose:* Under evaluation in Pediatric AIDS Clinical Trial Group protocol 332.

*Pediatric dose:* 1 mg per kg of body weight every 12 hours (up to weight of 30 kg).

*Adolescent/Adult dose:* Body weight ≥60 kg: 40 mg twice daily. Body weight <60 kg: 30 mg twice daily.

*Zerit XR capsules (adult dose):* Body weight ∃60 kg: 100 mg once daily. Body weight <60 kg: 75 mg once daily.

**Major Toxicities**
*More common:* Headache, gastrointestinal disturbances, and skin rashes.

*Less common (more severe):* Peripheral neuropathy and pancreatitis. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.

*Rare:* Increased liver enzymes.

**Drug Interactions**
- Drugs that decrease renal function could decrease clearance.
- Should not be administered in combination with ZDV (poor antiretroviral effect).

**Special Instructions**
- Can be administered with food.
- Need to decrease dose in patients with renal impairment.
- For oral solution: shake well and keep refrigerated; solution stable for 30 days.

## *Tenofovir (Viread®)*

**URL: Link to Pediatric Antiretroviral Drug Information**

*Preparations:* Tablets: 300 mg

**Dosage**
*Neonatal dose:* Unknown

*Pediatric dose:* Safety and effectiveness in pediatric patients have not been established. Current indication is for patients 18 years of age and older. Phase I study in pediatric patients is underway.

*Adult dose:* 300 mg once daily.

**Major Toxicities**
*More common:* Nausea, diarrhea, vomiting and flatulence..

*Less common (more severe):* Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported with the use of nucleoside analogs.

*Rare (unknown)*: Tenofovir caused bone toxicity (osteomalacia and reduced bone density) in animals when given in high doses. These effects have not been seen in adult patients taking tenofovir for up to one year. It is not known if these effects will be seen in persons taking tenofovir for more than one year or in children. Evidence of renal toxicity including increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calcuria and decreases in serum phosphate has been observed in animal studies at high exposure levels. Tenofovir-associated renal toxicity has not been observed in clinical studies of patients on treatment for up to one year. The long-term renal effects are not known but patients at risk should be closely monitored.

**Drug Interactions**
- Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir.
- ddI serum concentrations are increased when coadministered with tenofovir and patients should be monitored for ddI toxicity.
- Tenofovir should be given two hours before or one hour after ddI formulations.

**Special Instructions**
- Administer with food. High fat meal increases absorption.
- Decreased dosage should be used in patients with impaired renal function.
- Tenofovir should not be administered to patients with renal insufficiency (creatinine clearance <60 mL/min) until prescribing data is available in this patient population.
- Safety and effectiveness in pediatric patients has not been established.

## *Zalcitabine (ddC, HIVID®)*

**URL: Link to Pediatric Antiretroviral Drug Information**

*Preparations: Tablets:* 0.375 and 0.75 mg.

**Dosage**
*Neonatal dose:* Unknown
*Pediatric usual dose:* 0.01 mg per kg of body weight every eight hours.
*Adolescent/Adult dose:* 0.75 mg three times a day.

**Major Toxicities**
*More common:* Headache, gastrointestinal disturbances, and malaise.

*Less common (more severe):* Peripheral neuropathy, pancreatitis, hepatic toxicity, oral ulcers, esophageal ulcers, hematologic toxicity, and skin rashes. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.

**Drug Interactions**
- Antacids decrease absorption of ddC.
- Cimetidine, amphotericin, foscarnet, and aminoglycosides may decrease renal clearance of ddC.
- Concomitant use with ddI is not recommended because of the increased risk of peripheral neuropathy.
- Intravenous pentamidine increases the risk for pancreatitis; do not use concurrently.

**Special Instructions**
- Because the presence of food may decrease the rate and extent of absorption, it is recommended that ddC be administered on an empty stomach (one hour before or two hours after a meal).
- Decrease dosage in patients with impaired renal function.

## *Zidovudine (ZDV, AZT, Retrovir®)*

**URL: Link to Pediatric Antiretroviral Drug Information**

*Preparations:Syrup:* 10 mg/mL; *Capsules:* 100 mg; *Tablets:* 300 mg; Concentrate for injection/for intravenous infusion: 10 mg/mL.

*Tablets in combination with lamivudine:* COMBIVIR- 300 mg zidovudine and 150 mg lamivudine.

*Tablets in combination with lamivudine and abacavir:* TRIZIVIR- 300 mg zidovudine, 150 mg lamivudine, and 300 mg abacavir.

**Dosage**

*Dose for premature infants:* (Standard neonatal dose may be excessive in premature infants.) 1.5 mg per kg of body weight (intravenous) or 2 mg per kg of body weight (oral) every 12 hours increased to every eight hours at two weeks of age (neonates ∃30 weeks gestational age) or at four weeks (neonates < 30 weeks gestational age).

*Neonatal/Infant dose (infants aged <90 days):*
*Oral:* 2 mg per kg of body weight every six hours.
*Intravenous:* 1.5 mg per kg of body weight every six hours.

*Pediatric usual dose: Oral:* 160 mg per $m^2$ of body surface area every eight hours. Intravenous (intermittent infusion): 120 mg per $m^2$ of body surface area every six hours. *Intravenous (continuous infusion):* 20 mg per $m^2$ of body surface area per hour.
*Pediatric dosage range:* 90 mg per $m^2$ of body surface area to 180 mg per $m^2$ of body surface area every six to eight hours.

*Adolescent/Adult dose:* 200 mg three times a day or 300 mg twice daily.

*Adolescent/Adult dose of TRIZIVIR:* one tablet twice daily.

**Major Toxicities**

*More common:* Hematologic toxicity, including granulocytopenia and anemia, and headache.

*Less common:* Myopathy, myositis, and liver toxicity.

*Unusual (severe):* Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.

**Drug Interactions**

- Increased toxicity may be observed with concomitant administration of the following drugs (therefore, more intensive toxicity monitoring may be warranted): ganciclovir, interferon-alpha, TMP/SMX, acyclovir, and other drugs that can be associated with bone marrow suppression.
- The following drugs may increase ZDV concentrations (and therefore potential toxicity): probenecid, atovaquone, methadone, valproic acid, and fluconazole.
- Decreased renal clearance may be observed with co-administration of cimetidine (may be significant in patients with renal impairment).
- ZDV metabolism may be increased with coadministration of rifampin and rifabutin (clinical significance unknown); clarithromycin may decrease concentrations of ZDV probably by interfering with absorption (preferably administer four hours apart).
- Ribavirin decreases the intracellular phosphorylation of ZDV (conversion to active metabolite).
- Phenytoin concentrations may increase or decrease.
- Should not be administered in combination with d4T (poor antiretroviral effect).

**Special Instructions**

- Can be administered with food (although the manufacturer recommends administration 30 minutes before or one hour after a meal).
- Decrease dosage in patients with severe renal impairment.
- Substantial granulocytopenia or anemia may necessitate interruption of therapy until marrow recovery is observed; use of erythropoietin, filgrastim, or reduced ZDV dosage may be necessary in some patients.
- Reduced dosage may be indicated in patients with substantial hepatic dysfunction.
- Infuse intravenous loading dose or intermittent infusion dose over one hour.
- For intravenous solution: dilute with 5% dextrose injection solution to concentration ≤4 mg/mL; refrigerated diluted solution is stable for 24 hours.
- Some experts in pediatric HIV infection use a dose of 180 mg per $m^2$ of body surface area every 12 hours when using in drug combinations with other antiretroviral compounds, but data on this dosing in children is limited.

# Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) * †

## *Delavirdine (DLV, Rescriptor®)*

**URL: Link to Pediatric Antiretroviral Drug Information**

*Preparations:* Tablets: 100 mg and 200 mg.

### Dosage

*Neonatal dose:* Unknown.

*Pediatric dose:* Unknown.

*Adolescent/Adult dose:* 400 mg three times a day or 600 mg twice daily (investigational).

### Major Toxicities

*More common:* Headache, fatigue, gastrointestinal complaints, and rash (may be severe).

### Drug Interactions

- Metabolized in part by hepatic cytochrome P450 3A (CYP3A). There could potentially be multiple drug interactions.§
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- DLV decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. DLV is not recommended for concurrent use with antihistamines (i.e., astemizole or terfenadine), sedative-hypnotics (i.e., alprazolam, midazolam, or triazolam), calcium channel blockers (i.e., nifedipine), ergot alkaloid derivatives, amphetamines, cisapride, or warfarin.
- DLV clearance is increased, resulting in substantially reduced concentrations of DLV, with concurrent use of rifabutin, rifampin, or anticonvulsants (i.e., phenytoin, carbamazepine, or phenobarbital). Concurrent use is not recommended.
- Absorption of DLV is decreased if given with antacids or histamine$_2$ receptor antagonists.
- Increased trough concentrations of DLV if given with ketoconazole or fluoxetine; increased levels of both drugs if DLV is given with clarithromycin.
- DLV increases levels of dapsone and quinidine.
- Administration with protease inhibitors: decreases metabolism of SQV and IDV, resulting in a significant increase in SQV and IDV concentrations and a slight decrease in DLV concentrations.

### Special Instructions

- Can be administered with food.
- Should be taken one hour before or one hour after ddI or antacids.
- The 100 mg tablets can be dissolved in water and the resulting dispersion taken promptly. However, the 200 mg tablets should be taken as intact tablets, because they are not readily dispersed in water.

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* Information in this appendix is not all-inclusive. Complete and detailed prescribing and toxicity information on these drugs is available from the drug companies and should be reviewed by the health care provider before prescribing these drugs.

† Adolescents in early puberty (Tanner I-II) should be dosed using pediatric schedules, whereas those in late puberty (Tanner Stage V) should be dosed using adult schedules. Youth who are in the midst of their growth spurt (Tanner III females and Tanner IV males) should be closely monitored for medication efficacy and toxicity when choosing adult or pediatric dosing guidelines

§ Drugs metabolized by the hepatic cytochrome P450 enzyme system have the potential for significant interactions, some of which may be life-threatening with multiple drugs. These interactions are outlined in detail in prescribing information available from the drug companies. These interactions will not be reiterated in this document, and the health care provider should review those documents for detailed information. Before therapy with these drugs is initiated, the patient's medication profile should be carefully reviewed for potential drug interactions.

## *Efavirenz (DMP-266, EFV, Sustiva™)*

**URL: Link to Pediatric Antiretroviral Drug Information**

*Preparations: Capsules:* 50, 100, and 200 mg. Tablets: 600 mg.

**Dosage**

*Neonatal dose:* Unknown

*Pediatric dose:* Administered once daily.

*Body weight* 10 to <15 kg: 200 mg; 15 to <20 kg:250 mg; 20 to <25 kg: 300 mg; 25 to <32.5 kg: 350 mg; 32.5 to <40 kg: 400 mg; ≥40 kg:600 mg. There are currently no data available on the appropriate dosage for children under age three years.

*Adult/Adolescent dose:* 600 mg once daily

**Major Toxicities**

*More common:* Skin rash; central nervous system (somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria), primarily reported in adults; increased aminotransferase levels, teratogenic in primates (use in pregnancy should be avoided and women of childbearing potential should undergo pregnancy testing before initiating therapy).

**Drug Interactions**

- Mixed inducer/inhibitor of cytochrome P450 3A4 enzymes; concentrations of concomitant drugs can be increased or decreased depending on specific enzyme pathway involved.
- Not recommended for concurrent use: antihistamines (i.e., astemizole or terfenadine), sedative-hypnotics (i.e., midazolam or triazolam), cisapride, or ergot alkaloid derivatives.
- Drug interactions requiring careful monitoring if coadministered: warfarin (levels potentially increased or decreased); ethinyl estradiol (levels potentially increased; while of uncertain clinical significance, a reliable method of barrier contraception should be used in addition to oral contraceptives).
- Enzyme inducers such as rifampin, rifabutin, phenobarbital and phenytoin may decrease EFV concentrations; clinical significance is unknown.
- EFV is highly plasma protein bound, and has the potential for drug interactions with other highly proteinbound drugs (i.e., phenobarbital and phenytoin).
- Clarithromycin levels are decreased while the levels of its metabolite are increased; alternatives to clarithromycin, such as azithromycin, should be considered. Other macrolide antibiotics have not been studied in combination with EFV.
- Numerous drug interactions when EFV is administered in combination with protease inhibitors: Coadministration decreases levels of SQV (area under the curve [AUC] decreased by 50%) and IDV (AUC decreased by 31%). Coadministration of SQV as a sole PI is not recommended; IDV dose should be increased if given with EFV (for adults, 1000 mg every eight hours). Coadministration increases levels of both RTV and EFV (AUC increased by 20% for both), and is associated with a higher frequency of adverse clinical and laboratory findings; monitoring of liver enzymes is recommended if coadministered. Coadministration increases levels of NFV (AUC increased by 20%) but no dose adjustment is needed. EFV lowers LPV/r plasma concentrations and higher doses of LPV/r are recommended when used in combination.

**Special Instructions**

- Efavirenz can be taken with and without food. The relative bioavailability of EFV was increased by 50% (range 11-126%) following a high fat meal (1070 kcal, 82 grams fat, 62% of calories from fat - this is equivalent to an intake of 8.2 Milky Way candy bars in one sitting). Because there is no information on safety of EFV when given above the recommended dose, administration with a high fat meal should be avoided due to the potential for increased absorption.
- Capsules may be opened and added to liquids or foods, but EFV has a peppery taste; grape jelly has been used to disguise the taste.
- Bedtime dosing is recommended, particularly during the first two to four weeks of therapy, to improve tolerability of central nervous system side effects.

***Nevirapine (NVP, Viramune®)***
**URL: Link to Pediatric Antiretroviral Drug Information**

*Preparations: Suspension:* 10 mg/mL; Tablets: 200 mg.

**Dosage**
NVP is initiated at a lower dose and increased in a step-wise fashion. This allows induction of cytochrome P450 3A which results in increased clearance of drug. The occurrence of rash may be diminished by the stepwise increase in dosage. The following suggested incremental increases in dose are given for days on treatment (not age).

*Neonatal dose (through age two months):* Under study in Pediatrics AIDS Clinical Trial Group protocol 356: 5 mg/kg of body weight or 120 mg/m$^2$ of body surfurce area once daily for 14 days, followed by 120 mg/m$^2$ of body surface area every 12 hours for 14 days, followed by 200 mg/m$^2$ of body surface area every 12 hours.

*Pediatric dose:* * 120-200 mg/m$^2$ every 12 hours.
*Note:* Initiate therapy with 120 mg/m$^2$ (maximum 200 mg) administered once daily for 14 days. Increase to full dose (120-200 mg/m$^2$) administered every 12 hours (maximum 200 mg every 12 hours) if no rash or other untoward effects.

OR

7 mg/kg every 12 hours < eight years of age

4 mg/kg every 12 hours > eight years of age

*Note:* Initiate therapy with daily dose for 14 days and increase to full dose if no rash or other untoward effects.

*Adolescent/Adult dose:* 200 mg every 12 hours.
*Note:* Initiate therapy with 200 mg given once daily for the first 14 days. Increase to full dose administered every 12 hours if there is no rash or other untoward effects.

**Major Toxicities** (continuous dosing, not single dose regimens)

*More common:* (similar to adults) Skin rash (some severe, requiring hospitalization, and life-threatening, including Stevens-Johnson syndrome, toxic epidermal necrolysis), fever, nausea, headache, and abnormal liver function tests.

*Less common:* Inflammation of the liver (hepatitis), which rarely may lead to severe and life threatening and in some cases fatal liver damage, and very rarely fatal liver failure and granulocytopenia. Hypersensitivity reactions (including, but not limited to, severe rash or rash accompanied by fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise and/or significant hepatic abnormalities).

**Drug Interactions**
- Induces hepatic cytochrome P450 3A (CYP3A); autoinduction of metabolism occurs in two to four weeks with a 1.5fold to twofold increase in clearance. There could potentially be multiple drug interactions. **
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

* The majority of clinical trials involving infants and children utilized the 120-200 mg/m$^2$ dosing regimen. The new FDA approved regimen, which uses mg/kg dosing, is based on pharmacokinetic modeling designed to achieve similar plasma concentrations as dosing of 150 mg/m$^2$. NVP clearance is highest during the first two years of life, decreasing gradually after eight to 12 years of age and approaching adult clearance rates. The new dosing regimen accounts for the changes in clearance that occurs after eight years of age. However, the changes in clearance are gradual and the new mg/kg dosing regimen results in an abrupt 43% decrease in dose size when the 8$^{th}$ birthday is reached. Some clinicians may prefer the mg/m$^2$ dosing that was utilized in clinical trials.

** Drugs metabolized by the hepatic cytochrome P450 enzyme system have the potential for significant interactions, with multiple drugs. Some of which may be life-threatening. These interactions are outlined in detail in prescribing information available from the drug companies. These interactions will not be reiterated in this document, and the health care provider should review those documents for detailed information. Before therapy with these drugs is initiated, the patient's medication profile should be carefully reviewed for potential drug interactions.

- *Administration with PIs:* IDV and SQV (hard and soft gel formulations) concentrations are decreased significantly (approximately 25%-30%) when administered with NVP. SQV-HGC (Invirase) is not recommended for use in children and is recommended only in combination with RTV in adults. The adult guidelines recommend that IDV doses be increased by 20% when administered in combination with NVP, while recommending standard doses of NFV or RTV in combination with NVP. Data on specific dosing adjustments in pediatric patients for both IDV and NFV are lacking. NVP lowers LPV/r concentrations and higher doses of LPV/r are recommended when used in combination.
- Antifungals: NVP significantly reduces ketoconazole concentrations and these drugs should not be use concomitantly. If indicated, an alternate antifungal agent, such as fluconazole, should be used.
- Rifampin/Rifabutin: Rifampin significantly decreases NVP concentrations. It is not recommended that these drugs be used together. Rifabutin has less of an effect on NVP concentrations.
- Methadone: Patients on methadone maintenance may experience narcotic withdrawal symptoms when NVP is added to their regimen. If withdrawal symptoms occur, methadone doses should be increased and titrated to patient response.
- Anticonvulsants and psychotropics: There are no data on the extent of drug interactions with the anticonvulsants phenobarbital, phenytoin, and carbamazepine. Serum concentrations of these agents should be monitored. Many of the psychotropics are metabolized by similar metabolic pathways as NVP and may interact; patients should be monitored carefully when these medications are used concomitantly.
- Oral contraceptives: NVP may reduce plasma concentrations of oral contraceptives and other hormonal contraceptives. Oral contraceptives should not be the only means of birth control when used in patients on NVP.

**Special Instructions**

- Can be administered with food.
- May be administered concurrently with ddI.
- NVP-associated skin rash usually occurs within the first six weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase dose until rash resolves. NVP should be discontinued immediately in patients who develop severe rash or a rash accompanied by constitutional symptoms (i.e., fever, oral lesions, conjunctivitis, or blistering).
- Severe, life-threatening and in some cases fatal, hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure, has been reported in NVP-treated patients. Increased serum transaminase levels or a history of hepatitis B or C infection prior to starting NVP are associated with higher risk for hepatic adverse events. The majority of cases have occurred during the first 12 weeks of NVP therapy, and frequent and intensive clinical and laboratory monitoring, including liver function tests, is important during this time period. However, about one third of cases occurred after 12 weeks of treatment, so continued periodic monitoring of liver function tests is needed. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure; patients with symptoms or signs of hepatitis should have liver function tests performed. Patients should be instructed to contact their HIV specialist if signs or symptoms develop to determine the need for evaluation. NVP should be permanently discontinued and not restarted in patients who develop clinical hepatitis.
- For suspension: Must be shaken well; store at room temperature.

# Protease Inhibitors (PIs) * † §

## *Amprenavir (APV, Agenerase™)*

**URL: Link to Pediatric Antiretroviral Drug Information**

*Preparations: Pediatric oral solution:* 15mg/mL; *Capsules:* 50 and 150mg.

**Dosage**

*Neonatal/infant dose:* Not recommended in children <4 years of age.

*Pediatric/Adolescent dose (<50kg):* For children 4-12 years of age or 13-16 years olds weighing less than 50 kg: *Oral Solution:* 22.5 mg/kg twice daily hours or 17mg/kg three times daily (maximum daily dose 2,800 mg). *Capsules:* 20 mg/kg twice daily or 15 mg/kg three times daily (maximum daily dose 2,400 mg).

*Adult dose:* 1,200 mg (eight 150 mg capsules) bid

*Combination with ritonavir (adults):* APV 600 mg + RTV 100 mg twice daily, or APV 1200 mg + RTV 200 mg once daily

**Major Toxicities**

*More common:* Vomiting, nausea, diarrhea, perioral parethesias, and rash.

*Less common (more severe):* Life-threatening rash, including Stevens-Johnson syndrome in 1% of patients.

*Rare:* Increased cholesterol levels, new onset diabetes mellitus, hyperglycemia, exacerbation of preexisting diabetes mellitus, hemolytic anemia, and spontaneous bleeding in hemophiliacs.

**Drug Interactions**

- APV is a substrate for and inhibitor of the cytochrome P450 isoenzyme CYP3A4. There could potentially be multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- Coadministering EFV and APV lowers levels of APV 39% *[123]*.
- APV should not be administered concurrently with astemizole, bepridil, cisapride, dihydroergotamine, ergotamine, midazolam, rifampin and triazolam.
- Although no interaction studies have been conducted, serious drug interactions could occur between amiodarone, lidocaine, tricyclic antidepressants, quinidine and warfarin. It is recommended that the concentration of these drugs be monitored when administered concomitantly with APV.
- Rifampin has been found to reduce plasma concentrations of APV (decreased AUC 82%) and should not be used with APV. APV has no significant effect on rifampin plasma levels.
- The AUC of rifabutin is increased by 193% when given in combination with APV. The dose of rifabutin should be reduced by at least half the recommended dose when given in combination with APV.
- Coadministration of APV with sildenafil (Viagra) is likely to result in increased sildenafil concentrations and patients should be advised that they may be at an increased risk for sildenafil-associated adverse events, including hypotension, visual changes, and priapism.
- The FDA approved formulation of APV contains 46 IU vitamin E/ml of oral solution and 109 IU vitamin E-150 mg capsule. The recommended dose of APV results in a dose of 138 IU/kg/day of vitamin E using the oral solution with a maximum dose of 8,587 IU vitamin E per day. Patients receiving the recommended adult dose of APV in capsule form receive 1,744 IU/day of vitamin E. In comparison, the daily recommended dose for vitamin E in children is 10 IU per day and in adults 30 IU per day. Excess ingestion or administration of vitamin E has been associated with creatinuria, decreased platelet aggregation, impaired wound healing, hepatomegaly, prolongation of the Prothrombin Time and the potentiation of vitamin K deficiency coagulopathy. High dose vitamin E may increase the hypoprothrombinemic response to drugs such

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* Information in this appendix is not all inclusive. Complete and detailed prescribing and toxicity information on these drugs is available from the drug companies and should be reviewed by the health care provider before prescribing these drugs.

† Adolescents in early puberty (Tanner I-II) should be dosed using pediatric schedules, whereas those in late puberty (Tanner Stage V) should be dosed using adult schedules. Youth who are in the midst of their growth spurt (Tanner III females and Tanner IV males) should be closely monitored for medication efficacy and toxicity when choosing adult or pediatric dosing guidelines.

§ Data in children is limited, and doses may change as more information is obtained about the pharmacokinetics of these drugs in children.

as warfarin and dicumarol and concurrent use of vitamin E doses >400 IU/day should be avoided in patients taking oral anticoagulants. Patients taking APV should be advised not to take supplemental vitamin E *[124-128]*.

- The liquid formulation of APV contains propylene glycol in a concentration that exceeds WHO standards for use in infants. The serum half-life of propylene glycol in neonates is prolonged at 16.9 hours compared to five hours in adults, due to the immaturity of alcohol dehydrogenase enzyme activity in young infants. High levels of propylene glycol have been associated with hyperosmolarity, lactic acidosis, seizures, and respiratory depression *[129]*.
- The efficacy of hormonal contraceptives may be reduced in patients receiving APV. Alternate or additional methods of birth control should be coadministered if coadministering with hormonal methods of birth control.
- Other medications that are substrates, inhibitors, or inducers of CYP3A4 could also potentially interact with APV. See the product information for Agenerase for complete list of other drugs, which may potentially interact with APV.
- APV is a sulfonamide. The potential for cross sensitivity between drugs in the sulfonamide class and APV is unknown. APV should be used with caution in patients with sulfonamide allergy.

**Special Instructions**

- APV should not be used in children less than four years of age because of the lack of data in children < 4 years of age, the paucity of data in children in general, the uncertain impact of extremely high doses of vitamin E, and the propylene glycol content of the oral liquid preparation.
- The oral solution and capsule formulation are not interchangeable on a mg per mg basis. The oral bioavailability of the oral solution is 14% less than that of the capsule.
- APV may be taken with or without food, but should not be given with a high fat meal (i.e., 6.7 Milky Way bars) as there is a 21% decrease in the AUC when APV is administered after a high fat meal of 67 grams of fat compared with the fasting state.
- Patients taking antacids (or ddI) should take APV at least one hour before or after antacid (or ddI) use.

## *Indinavir (IDV, Crixivan®)*

**URL: Link to Pediatric Antiretroviral Drug Information**

*Preparations:* Capsules: 200 and 400 mg.

**Dosage**

*Neonatal dose:* Unknown. Due to side effect of hyperbilirubinemia, should not be given to neonates until further information is available.

*Pediatric dose:* Under study in clinical trials: 500 mg per $m^2$ of body surface area every eight hours. Patients with small body surface areas may require lower doses (300-400 mg/$m^2$ every 8 hours).

*Adolescent/Adult dose:* 800 mg every eight hours.

*Combination with ritonavir (adults):* IDV 400 mg + RTV 400 mg twice daily, or IDV 800 mg + RTV 200 mg twice daily

*Combination with efavirenz (adults):* IDV 1000 mg three times daily + EFV 600 mg once daily

**Major Toxicities**

*More common:* Nausea, abdominal pain, headache, metallic taste, dizziness, and asymptomatic hyperbilirubinemia (10%).

*Less common (more severe):* Nephrolithiasis (4%) and exacerbation of chronic liver disease.

*Rare:* Spontaneous bleeding episodes in hemophiliacs, hyperglycemia, ketoacidosis, diabetes, and hemolytic anemia.

**Drug Interactions**

- Cytochrome P450 3A4 (CYP3A4) responsible for metabolism. There could potentially be multiple drug interactions. ¶

¶ Drugs metabolized by the hepatic cytochrome P450 enzyme system have the potential for significant interactions, some of which may be life-threatening, with multiple drugs. These interactions are outlined in detail in prescribing information available from the drug companies. These interactions will not be reiterated in this document, and the health care provider should review those documents for detailed information. Before therapy with these drugs is initiated, the patient's medication profile should be carefully reviewed for potential drug interactions.

- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- IDV decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. IDV is not recommended for concurrent use with antihistamines (i.e., astemizole or terfenadine); cisapride; ergot alkaloid derivatives; or sedative-hypnotics (i.e., triazolam or midazolam).
- IDV levels are significantly reduced with concurrent use of rifampin. Concurrent use is not recommended.
- Rifabutin concentrations are increased, therefore a dose reduction of rifabutin to half the usual daily dose is recommended.
- Ketoconazole and itraconazole cause an increase in IDV concentrations (consider reducing adolescent/adult IDV dose to 600 mg every eight hours).
- Coadministration of clarithromycin increases serum concentration of both drugs (dosing modification not needed).
- Coadministration of NVP or EFV may decrease IDV serum concentration.
- Administration with other PIs: coadministration with NFV increases concentration of both drugs; coadministration with SQV increases concentration of SQV.

**Special Instructions**

- Administer on an empty stomach one hour before or two hours after a meal (or can take with a light meal).
- When given in combination with RTV, meal restrictions are no longer necessary.
- Adequate hydration required to minimize risk of nephrolithiasis (at least 48 oz of fluid daily in adult patients).
- If coadministered with ddI, give at least one hour apart on an empty stomach.
- Decrease dose in patients with hepatic insufficiency.
- Capsules are sensitive to moisture and should be stored in original container with desiccant.

## *Lopinavir/Ritonavir (Kaletra™, ABT 378, LPV/RTV)*

**URL: Link to Pediatric Antiretroviral Drug Information**

Coformulation of lopinavir and ritonavir: RTV acts as a pharmacokinetic enhancer, not as an antiretroviral agent. It does this by inhibiting the metabolism of lopinavir and increasing lopinavir plasma concentrations.

*Preparations:* Pediatric oral solution: 80 mg lopinavir and 20 mg ritonavir per mL; Capsules: 133.3 mg lopinavir/33.3 mg RTV.

**Dosage**

*Neonatal dose:* No pharmacokinetic data on dosing children less than six months of age.

- For individuals not receiving concomitant nevirapine or efavirenz:

Pediatric dose

| Six months to 12 years of age (without NVP or EFV) | |
|---|---|
| 7 to < 15 kg | 12 mg per kg lopinavir/3 mg per kg ritonavir twice daily with food. |
| 15 to 40 kg | 10 mg per kg lopinavir/2.5 mg per kg ritonavir twice daily with food. |
| > 40 kg | 400 mg lopinavir/100 mg ritonavir (three capsules or 5 mL) twice daily with food (same as adult dose). |

OR

230 mg per $m^2$ lopinavir/57.5 mg per $m^2$ ritonavir twice daily with food, up to a maximum of 400 mg lopinavir/100 mg RTV.

*Adult/Adolescent dose:* 400 mg lopinavir/100 mg ritonavir (three capsules or 5 mL) twice daily with food.

- For individuals receiving concomitant NVP or EFV (which induce lopinavir metabolism, reduce plasma levels and require increased lopinavir/ritonavir dosing) and/or treatment-experienced patients where reduced susceptibility to lopinavir is suspected (such as those with prior treatment with other PIs):

*Pediatric dose:*

| Six months to 12 years of age (with NVP or EFV) | |
|---|---|
| 7 to < 15 kg | 13 mg per kg lopinavir/3.25 mg per kg ritonavir twice daily with food. |
| 15 to 50 kg | 11 mg per kg lopinavir/2.75 mg per kg ritonavir twice daily with food. |
| > 50 kg | 533 mg lopinavir/133 mg ritonavir (four capsules or 6.5 mL) twice daily with food (same as adult dose). |

OR

300 mg per $m^2$ lopinavir/75 mg per $m^2$ ritonavir twice daily with food up to a maximum of 533 mg lopinavir/133 mg ritonavir.

*Adult/Adolescent dose:* 533 mg lopinavir/133 mg ritonavir (four capsules or 6.5 mL) twice daily with food.

*Note:* Although pediatric clinical trials utilized the mg per $m^2$ body surface area dosing, the FDA-approved doses are based on a mg per kg body weight dosage. The 230 mg per $m^2$ lopinavir/57.5 mg per $m^2$ RTV twice daily regimen without NVP or EFV and the 300 mg per $m^2$ lopinavir/75 mg per $m^2$ ritonavir twice daily regimen with concomitant NVP or EFV resulted in lopinavir concentrations similar to those obtained in adults receiving the 400 mg lopinavir/100 mg ritonavir twice daily regimen (without concomitant NVP or EFV). The pediatric trials were done in NNRTI naïve patients and there is little data in heavily pre-treated pediatric patients. In treatment-experienced patients where reduced susceptibility to lopinavir is suspected, higher doses may be required but there is little data to make definitive dosing recommendations at this time.

**Major Toxicities**

*More common:* Diarrhea, headache, asthenia, and nausea and vomiting. Increase in blood lipids (cholesterol and triglycerides), and rash in patients receiving lopinavir/ritonavir with other antiretroviral drugs.

*Rare:* Spontaneous bleeding episodes in hemophiliacs, pancreatitis, hyperglycemia, ketoacidosis, diabetes, and hepatitis.

**Drug Interactions**

- Lopinavir/ritonavir is extensively metabolized by hepatic cytochrome P450 3A (CYP3A). There could potentially be multiple drug interactions.[*]
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- Drugs that should not be coadministered with lopinavir/ritonavir include: antiarrhythmics (i.e., flecainide, propafenone); cisapride; neuroleptics (i.e., pimozide); ergot alkaloid derivatives; antihistamines (i.e., astemizole, terfenadine); sedative-hypnotics (i.e., midazolam, triazolam); HMG-COA reductase inhibitors (i.e., lovastatin, simvastatin); rifampin and St. John's wort.
- EFV and NVP induce the metabolism of lopinavir and decrease plasma concentrations. A dose increase of lopinavir/ritonavir is recommended (see dosage section).
- Anticonvulsant drugs including carbamazepine, phenytoin, and phenobarbital increase CYP3A activity, leading to increased clearance and, therefore, lower levels of lopinavir, and should be used with caution.
- Dexamethasone decreases lopinavir serum concentrations. Use with caution.
- Lopinavir/ritonavir increases serum concentrations of some HMG-CoA reductase inhibitors (i.e., atorvastatin, cerivastatin). Pravastatin and fluvastatin are preferred alternative agents.
- Lopinavir/ritonavir increases serum clarithromycin concentration and clarithromycin dose adjustment is recommended in patients with impaired renal function (CrCl 30-60 mL/min decrease clarithromycin dose by 50%; CrCl < 30 mL/min decrease clarithromycin dose by 75%).
- Lopinavir/ritonavir increases rifabutin and rifabutin metabolite concentrations, and dose reduction of rifabutin by at least 75% of the usual dose is recommended.

[*] Drugs metabolized by the hepatic cytochrome P450 enzyme system have the potential for significant interactions with multiple drugs, some of which may be life-threatening. These interactions are outlined in detail in prescribing information available from the drug companies. These interactions will not be reiterated in this document, and the health care provider should review those documents for detailed information. Before therapy with these drugs is initiated, the patient's medication profile should be carefully reviewed for potential drug interactions.

- Lopinavir/ritonavir increases sildenafil (Viagra) serum concentrations. Reduce dose of sildenafil and monitor for toxicity.
- Lopinavir/ritonavir increases serum concentrations of the antiarrhythmics amiodarone, bepridil, lidocaine (systemic) and quinidine. Monitoring of antiarrhythmic serum concentrations is recommended.
- Lopinavir/ritonavir may increase serum concentrations of the immunosuppressant agents cyclosporine, tacrolimus, and rapamycin. Monitor serum concentrations of these agents when coadministered.
- Lopinavir/ritonavir increases serum concentrations of dihydropyridine calcium channel blockers (i.e., felodipine, nifedipine, nicardipine). Clinical monitoring is recommended.
- Lopinavir/ritonavir decreases methadone serum concentrations when coadministered. Patients should be closely monitored for withdrawal symptoms, and methadone dosage should be increased as necessary.
- Lopinavir/ritonavir increases serum concentrations of ketoconazole and itraconazole. High doses of these agents (>200 mg/day) are not recommended.
- Lopinavir/ritonavir decreases atovaquone concentrations. The clinical significance is unknown.
- Ethinyl estradiol levels are reduced by lopinavir/ritonavir, and alternative or additional methods of birth control should be used if coadministered with hormonal methods of birth control.
- Administration with other PIs: appropriate doses of lopinavir/ritonavir with APV, SQV, IDV, or additional RTV have not been established.
- Lopinavir/ritonavir oral solution contains 42.4% alcohol and can cause a disulfiram-like reaction when coadministered with disulfiram or metronidazole.

**Special Instructions**

- Administer with food. High fat meal increases absorption, especially of the liquid preparation.
- If coadministered with ddI, ddI should be given one hour before or two hours after lopinavir/ritonavir.
- Oral solution and capsules should be refrigerated. Can be kept at room temperature up to 77ºF (25ºC) if used within two months.

## *Nelfinavir (NFV, Viracept®)*

**URL: Link to Pediatric Antiretroviral Drug Information**

*Preparations: Powder for oral suspension:* 50 mg per one level gram scoop full (200 mg per one level teaspoon); *Tablets:* 250 mg tablet.

**Dosage**

*Neonatal dose:* Under study in Pediatric AIDS Clinical Trials Group protocol 353: 40 mg per kg of body weight every 12 hours.

*Pediatric dose:* Currently under review: 20 to 30 mg per kg of body weight three times a day is the FDA approved dose. However, doses as high as 45 mg/kg every 8 hours are routinely used. Twice daily dosing in pediatric patients is under study (50-55 mg/kg/dose) in older children (>6 years of age).

*Adolescent/Adult dose:* 1250 mg (5 tablets) twice daily or 750 mg (3 tablets) three times daily. Doses of 1500 mg (6 tablets) twice daily are under study in adults.

**Major Toxicities**

*More common:* Diarrhea.

*Less common:* Asthenia, abdominal pain, rash, and exacerbation of chronic liver disease.

*Rare:* Spontaneous bleeding episodes in hemophiliacs, hyperglycemia, ketoacidosis, and diabetes.

**Drug Interactions**

- NFV is in part metabolized by cytochrome P450 3A4 (CYP3A4). There could potentially be multiple drug interactions.*
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

* Drugs metabolized by the hepatic cytochrome P450 enzyme system have the potential for significant interactions, some of which may be life-threatening, with multiple drugs. These interactions are outlined in detail in prescribing information available from the drug companies. These interactions will not be reiterated in this document, and the health care provider should review those documents for detailed information. Before therapy with these drugs is initiated, the patient's medication profile should be carefully reviewed for potential drug interactions.

- NFV decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. NFV is not recommended for concurrent use with antihistamines (i.e., astemizole or terfenadine); cisapride; ergot alkaloid derivatives; certain cardiac drugs (i.e., quinidine or amiodarone); or sedative-hypnotics (i.e., triazolam or midazolam).
- NFV levels are greatly reduced with concurrent use of rifampin. Concurrent use is not recommended.
- Rifabutin causes less decline in NFV concentrations; if coadministered with NFV, rifabutin should be reduced to one half the usual dose.
- Estradiol levels are reduced by NFV, and alternative or additional methods of birth control should be used if coadministering with hormonal methods of birth control.
- Coadministration with DLV increases NFV concentrations twofold and decreases DLV concentrations by 50%. There are no data on coadministration with NVP, but some experts use higher doses of NFV if used in combination with NVP.
- Administration with other PIs: coadministration with IDV increases concentration of both drugs; coadministration with SQV increases concentration of SQV with little change in NFV concentration; coadministration with RTV increases concentration of NFV without change in RTV concentration.

**Special Instructions**

- Administer with meal or light snack.
- If coadministered with ddI, NFV should be administered two hours before or one hour after ddI.
- For oral solution: powder may be mixed with water, milk, pudding, ice cream, or formula (for up to six hours).
- Do not mix with any acidic food or juice because of resulting poor taste.
- Do not add water to bottles of oral powder; a special scoop is provided with oral powder for measuring purposes.
- Tablets readily dissolve in water and produce a dispersion that can be mixed with milk or chocolate milk; tablets also can be crushed and administered with pudding.

## *Ritonavir (RTV, Norvir®)*

**URL: Link to Pediatric Antiretroviral Drug Information**

*Preparations: Oral solution:* 80 mg/mL; *Capsules:* 100 mg

**Dosage**

*Neonatal dose:* Under study in Pediatric AIDS Clinical Trials Group protocol 354 (single dose pharmacokinetics).

*Pediatric usual dose:* 400 mg per $m^2$ of body surface area every 12 hours. To minimize nausea/vomiting, initiate therapy starting at 250 mg per $m^2$ of body surface area every 12 hours and increase stepwise to full dose over five days as tolerated.

*Pediatric dosage range:* 350 to 400 mg per $m^2$ of body surface area every 12 hours.

*Adolescent/Adult dose:* 600 mg twice daily. To minimize nausea/vomiting, initiate therapy starting at 300 mg twice daily and increase stepwise to full dose over five days as tolerated.

*Combination with saquinavir (Fortovase) (adults):* RTV 400-600 mg + SQV 400 mg twice daily

*Pharmacokinetic Enhancer:* Used at lower doses as pharmacokinetic enhancer of other protease inhibitors Doses most commonly used in adults are 200 mg every 12 hours to 400 mg every 12 hours when combined with other protease inhibitors.

**Major Toxicities**

*More common:*Nausea, vomiting, diarrhea, headache, abdominal pain, and anorexia.

*Less common:* Circumoral paresthesias and increase in liver enzymes.

*Rare:* Spontaneous bleeding episodes in hemophiliacs, pancreatitis, increased levels of triglycerides and cholesterol, hyperglycemia, ketoacidosis, diabetes, and hepatitis.

**Drug Interactions**

- RTV is extensively metabolized by hepatic cytochrome P450 3A (CYP3A). There could potentially be multiple drug interactions. *
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- Not recommended for concurrent use with analgesics (i.e., meperidine, piroxicam, or propoxyphene); antihistamines (i.e., astemizole or terfenadine); certain cardiac drugs (i.e., amiodarone, bepridil hydrochloride, encainide hydrochloride, flecainide acetate, propafenone, or quinidine); ergot alkaloid derivatives; cisapride; sedative-hypnotics (i.e., alprazolam, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam, or zolpidem); certain psychotropic drugs (i.e., bupropion hydrochloride, clozapine, or pimozide); rifampin; or rifabutin.
- Estradiol levels are reduced by RTV, and alternative or additional methods of birth control should be used if coadministering with hormonal methods of birth control.
- RTV increases metabolism of theophylline (levels should be monitored, and dose may need to be increased).
- RTV increases levels of clarithromycin (dose adjustment may be necessary in patients with impaired renal function); desipramine (dose adjustment may be necessary); and warfarin (monitoring of anticoagulant effect is necessary).
- RTV may increase or decrease digoxin levels (monitoring of levels is recommended).
- Drugs that increase CYP3A activity can lead to increased clearance and, therefore, lower levels of RTV include carbamazepine, dexamethasone, phenobarbital, and phenytoin (anticonvulsant levels should be monitored because RTV can affect the metabolism of these drugs as well).
- Administration with other PIs: coadministration with SQV and NFV increases concentration of these drugs with little change in RTV concentration.

**Special Instructions**

- Administration with food increases absorption and helps decrease gastrointestinal side effects.
- If RTV is prescribed with ddI, there should be two hours between taking each of the drugs.
- Oral solution must be kept refrigerated and stored in original container; can be kept at room temperature if used within 30 days. Limited shelf-life (six months). Use by product expiration date.
- To minimize nausea, therapy should be initiated at a low dose and increased to full dose over five days as tolerated.
- Techniques to increase tolerance in children:
  a. mixing oral solution with milk, chocolate milk, or vanilla or chocolate pudding or ice cream;
  b. dulling the taste buds before administration by chewing ice, giving popsicles or spoonfuls of partially frozen orange or grape juice concentrates;
  c. coating the mouth by giving peanut butter to eat before the dose; or
  d. administration of strong-tasting foods such as maple syrup, cheese, or strong-flavored chewing gum immediately after dose.

* Drugs metabolized by the hepatic cytochrome P450 enzyme system have the potential for significant interactions, some of which may be life-threatening, with multiple drugs. These interactions are outlined in detail in prescribing information available from the drug companies. These interactions will not be reiterated in this document, and the health care provider should review those documents for detailed information. Before therapy with these drugs is initiated, the patient's medication profile should be carefully reviewed for potential drug interactions.

### *Saquinavir (SQV, Invirase™ hard gel capsule and Fortovase™ soft gel capsule)*

**URL: Link to Pediatric Antiretroviral Drug Information**

*Preparations:* Soft gel capsules: 200 mg (preferred product); Hard gel capsules: 200 mg. Please note that Saquinavir-HGC (Invirase) is not recommended except in combination with ritonavir.

**Dosage**

*Neonatal dose:* Unknown.

*Pediatric dose:* Under study: 50 mg per kg body weight every 8 hours as single protease inhibitor therapy. 33 mg per kg body weight every 8 hours as usual therapy with nelfinavir.

*Adolescent/Adult dose:* Soft gel capsules: 1200 mg three times a day or 1600 mg twice daily.

**Major Toxicities**

*More common:* Diarrhea, abdominal discomfort, headache, nausea, paresthesias, and skin rash.

*Less common:* Exacerbation of chronic liver disease.

*Rare:* Spontaneous bleeding episodes in hemophiliacs, hyperglycemia, ketoacidosis, and diabetes.

**Drug Interactions**

- SQV is metabolized by the cytochrome P450 3A4 (CYP3A4) system in the liver, and there are numerous potential drug interactions. *
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- SQV decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. SQV is not recommended for concurrent use with antihistamines (i.e., astemizole or terfenadine); cisapride; ergot alkaloid derivatives, or sedative-hypnotics (i.e., midazolam or triazolam).
- SQV levels are significantly reduced with concurrent use of rifampin (decreases SQV levels by 80%), rifabutin (decreases SQV levels by 40%), and NVP (decreases SQV levels by 25%).
- SQV levels are decreased by carbamazepine, dexamethasone, phenobarbital, and phenytoin.
- SQV levels are increased by DLV and ketoconazole.
- SQV may increase levels of calcium channel blockers, clindamycin, dapsone, and quinidine. If used concurrently, patients should be closely monitored for toxicity.
- Administration with other PIs: coadministration with IDV, RTV, or NFV increases concentration of SQV with little change in concentration of the other drug.

**Special Instructions**

- Administer within two hours of a full meal to increase absorption.
- Concurrent administration of grapefruit juice increases SQV concentration.
- Sun exposure can cause photosensitivity reactions; therefore, sunscreen or protective clothing is recommended.
- Fortovase® and Invirase® are not bioequivalent and cannot be used interchangeably. Fortovase® is the recommended formulation.

* Drugs metabolized by the hepatic cytochrome P450 enzyme system have the potential for significant interactions, some of which may be life-threatening, with multiple drugs. These interactions are outlined in detail in prescribing information available from the drug companies. These interactions will not be reiterated in this document, and the health care provider should review those documents for detailed information. Before therapy with these drugs is initiated, the patient's medication profile should be carefully reviewed for potential drug interactions.

# Fusion Inhibitors

## *Enfuvirtide (Fuzeon ™, T-20)*

**URL: Link to Pediatric Antiretroviral Drug Information**

*Preparations:* Injection: lyophilized powder for injection 108 mg of enfuvirtide, when reconstituted with 1.1 ml sterile water to deliver 90 mg/ml.

*Convenience Kit:* 60 single use vials of Fuzeon (90mg strength), 60 vials of sterile water for injection, 60 reconstitution syringes (3ml), 60 administration syringes (1 ml), alcohol wipes.

**Dosage**

*Neonatal/infant dose*: Not approved for use in pediatric patients below the age of 6 years old.

*Pediatric/adolescent dose (6-16 years of age)*: 2 mg/kg twice daily, maximum dose 90 mg (1ml) twice daily injected subcutaneously into the upper arm, anterior thigh, or abdomen.

*Adult dose*: 90 mg (1ml) twice daily injected subcutaneously into the upper arm, anterior thigh, or abdomen.

**Major Toxicities**

*Most common:* Almost all patients (98%) get local injection site reactions including pain and discomfort, induration, erythema, nodules and cysts, pruritis, and ecchymosis. Usually mild to moderate in severity but can be more severe.

*Less common*: Increased rate of bacterial pneumonia (unclear association).

*Rare*: Hypersensitivity reactions including fever, nausea and vomiting, chills, vigors, hypotension, elevated liver transaminases. Immune-mediated reactions including primary immune complex reaction, respiratory distress, glomerulonephritis, and Guillan-Barre syndrome. Patients experiencing hypersensitivity reactions should seek immediate medical attention. Therapy should not be restarted following signs and symptoms consistent with hypersensitivity reactions.

**Drug Interactions**

There are no known significant drug interactions.

**Special Instructions**

- Patients or caregivers should be carefully instructed in proper technique for drug reconstitution and administration of subcutaneous injections. Fuzeon injection instructions are provided with convenience kits.
- Reconstituted vial should be allowed to stand until the powder goes completely into solution which could take up to 45 minutes.
- Once reconstituted, Fuzeon should be injected immediately or kept refrigerated in the original vial until use. Reconstituted Fuzeon must be used within 24 hours.
- Each injection should be given at a site different from the preceding injection site, and should not be injected into moles, scar tissue, bruises, or the navel.
- Careful monitoring for signs and symptoms of local infection or cellulitis should be done by both the patient/caregiver and health care provider.
- Patients/caregivers should be advised of the possibility of a hypersensitivy reaction and should discontinue treatment and seek immediate medical attention if the patient develops signs and symptoms consistent with a hypersensitivity reaction.